Practitioner's Docket No. MPI96-027CP2RCE2M

REMARKS

No claims have been amended in this response. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 are pending.

WITHDRAWN REJECTIONS

Applicants appreciate notification of the withdrawal of the rejection under 35 U.S.C. §112, first paragraph (written description); the rejections under 35 U.S.C. §§102(a) and 103(a) over Bleul et al.; and the non-statutory double-patenting rejection.

MAINTAINED REJECTION

The Rejection of Claims under 35 USC §103(a) Should Be Withdrawn

Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 were rejected by the Examiner under 35 U.S.C. §103(a) as unpatentable over Li et al. (U.S. Patent 6,025,154), in view of Li et al. (U.S. Patent 6,759,519), Raport et al. (*J. Biol. Chem.*, 271(29):17161-17166, 1996), Combadiere et al. (*J Leukocyte Biol.*, 60:147-152, 1996), Samson et al. 1996 (*Biochemistry*, 35:3362-3367, 1996), and Atchison et al. (*Science*, 274 :1924-1926, 1996), as evidenced by Wu et al. (*J. Exp. Med.* 186(8):1373-1381, 1997), and Samson et al. 1997 (*J. Biol. Chem.*, 272(40): 24934-24941, Oct. 1997).

Applicants traverse the rejection, and respectfully point out that the Examiner has mischaracterized and/or incompletely characterized the references relied upon for this rejection and in Applicants' rebuttal. Applicants will attempt to address these issues below. Please also see Applicants' arguments against this rejection, previously made of record particularly in Applicants' responses filed May 16, 2008 (pp. 10-14) and August 29, 2007 (pp. 6-11).

Raport et al. (*J. Biol. Chem.*, 1996) and Combadiere et al. (*J Leukocyte Biol.*, 1996)

In describing the disclosures of Samson (1996), Combadiere (1996) and Raport (1996) with respect to identification of ligands that bind and activate CCR5 (MIP-1α, MIP-1β, and RANTES), the Examiner stated:

> "Both Raport (p. 17166) and Combadiere (p. 151) teach that these ligands are known to suppress HIV-1 entry into cells, and indicate that CCR5 is the strongest candidate for a chemokine HIV receptor."

In response to this assertion, Applicants note that in the places cited by the Examiner, both Raport et al. and Combadiere et al. are citing an earlier publication of work done by Cocchi et al. (made of record in Information Disclosure Statement filed on Oct. 5, 2001 as citation AW2). Cocchi et al., published on December 15, 1995, described the identification of RANTES, MIP-1α, and MIP-1β as HIV-suppressive factors produced by CD8+ T cells (with no mention of CCR5). However, Applicants respectfully point out that Cocchi et al. makes the following statement:

> "[C]hemokine-mediated control of HIV may occur either directly, through their inherent anti-lentiretroviral activity, or indirectly, through their ability to chemoattract T cells and monocytes in the proximity of infection foci" (see, e.g., page 1814, second column, first full paragraph).

In addition, Cocchi et al. teaches that allowing RANTES, MIP-1α, and MIP-1β to bind to their receptor "may also have the opposite effect of providing, new uninfected targets for HIV infection" (please see Cocchi et al., p. 1814, 2nd and 3rd columns, paragraph spanning). Thus, Cocchi et al., (which is the basis for the Examiner's assertion of what Raport (1996) and Combadiere (1996) teach regarding CCR5 ligands and HIV), in combination with identification of CCR5 as a receptor for RANTES, MIP-1α, and MIP-1β, suggests that allowing chemokines to bind CCR5 may have the deleterious effect of attracting new T cell targets for HIV.

Atchison et al. (*Science*, 1996)

The Examiner also made a number of assertions about the disclosure of Atchison which are incorrect and/or incomplete, and which Applicants set out here to elucidate.

(1) The Examiner stated that:

"Atchison teaches that the second extracellular domain of CCR5 is sufficient for HIV-1 entry into cells. Additionally, Atchison provides several examples of proteins which contain the extracellular loop of CCR5 that also allow for HIV-1 entry. See for example Figure 3, note that "2555", which has the N-terminus of CCR2 (residues 1-44) fused to the remainder of CCR5 (residues 33-352) allows for HIV-1 entry." (emphasis added)

(2) The Examiner also stated that:

"Additionally, Atchison presents data indicating that a fusion protein wherein the N-terminal extracellular region of CCR2 (which does not act as an HIV coreceptor) is fused to the remaining part of the CCR5 receptor (which of course does act as an HIV coreceptor), including the second extracellular loop, has robust HIV coreceptor activity. See Figure 3, compare bar for 5555 (human CCR5) with 2555."

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Applicants respectfully submit that the Examiner is interpreting the results of Atchison incorrectly and/or is not considering the entirety of the data and conclusions presented by Atchsion, as follows.

Firstly, the assertion that Atchison teaches that the second extracellular domain is sufficient for HIV-1 entry into cells is plainly incorrect. Atchison et al. teaches that a fusion receptor, 2255, which contains extracellular loop 2 of CCR5, "repeatedly had no coreceptor function (2255, Fig. 3B)", (please see page 1925, first column, first full paragraph, and Figure 3B, 2255).

Since a fusion receptor containing the second extracellular loop had no HIV coreceptor function, one of skill in the art could not conclude that the second extracellular loop could, on its own (i.e., be sufficient to), confer coreceptor activity. However, Atchison et al. does distinctly point out that "simple substitution of the *NH_2-terminal segment* of CCR2B with the corresponding segment from human CCR5 (5222) conferred robust susceptibility to HIV-1 cell entry" (emphasis added). So, if anything, Atchison teaches that the N-terminus of CCR5 is sufficient to confer HIV coreceptor activity, and the second extracellular loop is neither sufficient nor necessary for HIV entry. In this way, Atchison directs the person of skill in the art to the amino terminal portion of CCR5 as important in HIV coreceptor activity.

Secondly, the implication that the HIV coreceptor activity of the 2555 CCR2/CCR5 chimera is due to the presence of the second extracellular loop in 2555 is flawed and incorrect. Applicants direct the Examiner's attention to Figure 3 and the results shown for chimeras 5555, 2555, and 2255. Note that chimera 2255 contains the second and third extracellular loops of CCR5, and yet shows almost no HIV coreceptor activity (see Fig. 3B, 2255). While the 2555 chimera referred to by the Examiner (which *has* extracellular loops 1, 2, and 3 of CCR5), does show HIV coreceptor activity, the 2255 chimera (which *also has* the second and third extracellular loops, *but is missing the first extracellular loop of CCR5*) "repeatedly had no coreceptor function" (page 1925, first column). From this, one of skill in the art cannot conclude that the second extracellular loop of CCR5 is what is responsible for conferring HIV coreceptor activity to the 2555 CCR2/CCR5 chimera, since another chimera that also contains the second extracellular loop of CCR5, the 2255 chimera, does not confer HIV coreceptor activity, and the 5222 chimera (having only the N-terminus of CCR5) does.

Atchison does not direct one of skill in the art toward the second loop of CCR5 for HIV coreceptor activity — if anything, Atchison directs the reader toward the N-terminus (as that is the portion of CCR5, which on its own, "conferred robust susceptibility to HIV"), and away from the second loop (as the 2255 chimera, containing the second loop of CCR5, has "no coreceptor function" despite abundant expression on the surface of cells examined). Atchison et al. teaches away from combining the cited references in order to arrive at the claimed invention, and in places that it does not specifically teach away, Atchison does not provide any guidance, teaching, suggestion, or motivation to make the combination of references cited by the Examiner.

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Rucker et al. (*Cell* 1996)

Applicants respectfully submit that the Examiner is also interpreting the results of Rucker et al. incorrectly and/or is not considering the entirety of the data and conclusions presented by Rucker, as follows. (Rucker et al. was cited by Applicants as support that art at the time of filing taught away from the claimed antibodies, pharmaceutical compositions, and kits. Please see, e.g., pp. 10-14 of previous arguments of record filed May 16, 2008.)

Firstly, the Examiner stated that Rucker et al. "concentrates on the role of the N-terminus of CCR5 in allowing HIV entry" (Page 5, first full paragraph of the 9/4/2008 Office action).

In asserting that Rucker et al. does not teach away from the combination of the cited references in order to arrive at antibodies having all of the claimed characteristics, the Examiner then stated that,

> "Additionally, Rucker teaches that chimera 25-13, which has the N-terminal region and second extracellular loop from CCR5, allows for HIV entry. See...Figure 5B which indicates entry of HIV is the same in CCR5- containing and 25-13-containing cells."

Applicants respectfully submit that the Examiner has not fully considered the data and/or conclusions presented in Rucker et al. For instance, the Examiner's discussion of Rucker's results in Figure 5B (page 6 of the 9/4/2008 Office action) does not consider all of the results displayed in that figure, nor the conclusions made by the authors. The Examiner stated that Figure 5B indicates that "entry of HIV is the same in CCR5-containing and 25-13-containing cells". However, the level of fusion shown for another chimera, called "25-05", is the same as for CCR5 and for 25-13. The 25-05 chimera does contain the N-terminus and third extracellular loop of CCR5, but it does not contain the second extracellular loop. Thus, this other chimera appears to have the same amount of HIV cofactor activity as both CCR5 and the 25-13 chimera cited by the Examiner — the difference is that the 25-05 chimera does not contain the second loop.

In addition, Figure 5B shows results for another second loop-containing chimera, 25-11, which has the first and second loops of CCR5, but not the N-terminus or the third extracellular loop – this chimera, having the second loop of CCR5, does not show robust fusion activity. However, the 25-05 and 25-13 chimeras, which each have the N-terminus of CCR5, have fusion activity. One of skill in the art would then be led to conclude (as the authors have) that the N-terminus may be important for HIV entry, but the second loop is not (see pages 443 and 444, quoted below). Applicants assert that the totality of the results shown in Figure 5B do not show that the second loop of CCR5 allows for HIV entry. In order for the skilled person to conclude as the Examiner is asserting (that Rucker et al. points to the second

extracellular loop), he or she would have to conclude the opposite of what is shown in Figure 5B and concluded by the authors.

Rucker et al. itself makes the following conclusions (page 443 and 444):

(1) "Our results indicate that the amino terminus of CCR5 plays an important role in virus entry. The amino-terminal domain of CCR5 was the only region that, when introduced into CCR2b, conferred M-tropic cofactor activity to the resulting chimera" (page 443, first column, first full paragraph, emphasis added); and

(2) "Introduction of the second loop from CCR5 into CCR2b failed to confer M-tropic cofactor function...Thus, the second loop appears to play little role in cofactor specificity." (page 444, first column, lines 5-10, emphasis added).

The second loop of CCR5 "failing to confer" HIV coreceptor activity in Rucker et al. teaches away from combination of the cited references in order to arrive at the claimed invention (where the claimed antibodies bind to the second extracellular loop of CCR5, among other claimed characteristics). Further, the second loop "[a]ppearing to play little role in" HIV coreceptor activity similarly does *not* indicate "that each of the extracellular loops is important for viral entry", as the Examiner has asserted (9/4/2008 Office action, page 6), and indeed teaches away from the combination of references/claimed invention. In places that it does not specifically teach away, Rucker et al. does not provide any guidance toward CCR5 antibodies with the characteristics as claimed. If anything, Rucker et al. directs the reader toward the amino terminus and/or the first extracellular loop (See page 444, first column, second full paragraph):

The Examiner went on to state:

"Clearly, it is uncontested that at the time the invention was made it was known that ligands to CCR5 block HIV. The most parsimonious explanation for this is that they occupy an important HIV entry site. Antibodies raised against this site, i.e. the second extracellular loop, would of course block ligand binding, and since they physically occupy the same site as those ligands which block HIV entry, the antibodies would also be expected to block HIV entry." (emphasis added)

Applicants point out that the explanation provided by the Examiner is apparently his opinion, based on the benefit of currently understood knowledge. Much of the basis the Examiner relies on in the statements above was not necessarily known at the time, and the art at the time appeared to teach away, as argued herein and in previous responses. For example, the Examiner has not cited art available at the time of

filing to support the assertion above that "they physically occupy the same site as those ligands which block HIV entry, the antibodies would also be expected to block HIV entry".

In addition, an alternative explanation at the time could have been that chemokine-activated CCR5 is internalized (internalization of ligand-bound receptors being a well-known phenomenon) into cells expressing it, thus removing HIV's access to CCR5 and suppressing infection. In addition, as Applicants have outlined above, Raport and Combadiere, cited as art in support of this obviousness rejection, refer to the work of Cocchi et al., who presented results showing that the chemokines MIP-1α, MIP-1β, and RANTES can suppress HIV infection. Cocchi et al. suggests, *inter alia*, that using chemokines to control HIV infection may act through activation of target cells to recruit T cells and monocytes to the affected area, possibly bringing more cells to be infected by HIV (see page 1814, second column). One of skill in the art at the time would have at least considered these potential deleterious effects of using the chemokines MIP-1α, MIP-1β, and RANTES to modulate HIV infection. Therefore, the Examiner has not shown that one of skill in the art would have found the teaching, suggestion, or motivation to combine the cited references in order to arrive at antibodies to CCR5 with all the claimed characteristics.

Furthermore, the Examiner apparently contradicted himself when he stated:

(1) that "Antibodies raised against this site, i.e. the second extracellular loop, would of course block ligand binding, and since they physically occupy the same site as those ligands which block HIV entry, the antibodies would also be expected to block HIV entry," and;

(2) then further stated "The examiner has not made an argument that antibodies that block chemokine binding inherently have the HIV-blocking property."

Apparently, the Examiner is confused as to whether antibodies which bind the second extracellular loop of CCR5 would "of course" block ligand binding and HIV infection. As Applicants have previously described, the work of Roschke et al. (please see, e.g., pages 13-14 of the May 16, 2008 response to OA, and page 10 of the August 29, 2007 response to OA) shows this not to be the case.

Accordingly, in absence of evidence to the contrary, Applicants assert that there is no credible scientific reasoning or evidence to support the Examiner's assertion that it would have been obvious to

(1) combine the screen of Li et al. to identify an antibody which binds CCR5 and inhibits chemokine binding to CCR5 with -

(2) a further screen to identify antibodies which also block HIV infection.

The cited references provide no teaching, suggestion, or motivation to combine the references in order to arrive at the claimed invention. Applicants additionally assert that a skilled artisan would not

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have been expected to succeed in generating an antibody to CCR5 containing both attributes as previously described. As indicated herein, the disclosures of Cocchi et al., Atchsion et al., and Rucker et al., when fully considered, either cast doubt on the assertion that one of skill would have had the motivation, suggestion or expectation of success to combine the references, or they directly teach away from the combination. Thus, the presently claimed invention is non-obvious over the cumulative reference teachings of the art cited by the Examiner.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims under 35 USC §103(a).

NEW REJECTION

The Rejection of Claims under 35 USC §102(e) Should Be Withdrawn

Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 were rejected under 35 USC 102(e) as being allegedly anticipated by Combadiere et al. (U.S. Patent Application Publication No. 2003/0195348, published 16 October 2003, filed 15 May 2003).

The Examiner asserted that Combadiere et al. (U.S. Patent Application Publication) teaches antibodies that have all of the characteristics of the claimed antibodies. Specifically, the Examiner pointed to paragraphs [0067-0069] of Combadiere et al., stating:

> "On pp. 7 – 9, Combadiere discusses **the antibodies** to CCR5 in more detail. At paragraphs [0067] - [0069], the reference teaches that **the antibodies** that bind CCR5 block HIV entry into human cells, and teaches that **the antibodies** are raised against any of the three extracellular loops of the receptor…At paragraph [0069] Combadiere teaches that **their antibodies** not only block HIV entry but also block binding of chemokines, i.e. the known ligands of the CCR5 receptor. Note particularly first sentence of this paragraph, which lists both of these as properties of the antibodies, and final sentence of this paragraph, which states that the antibodies can have any or all of the recited functions. As the reference **teaches raising antibodies against the second extracellular loop** of CCR5, and teaches that the antibodies block both HIV entry and ligand binding, it anticipates claim 158." (emphasis added)

Applicants respectfully traverse the foregoing rejection on the grounds that Combadiere *et al.* (U.S. Patent Application Publication) fails to teach or suggest each and every element of the claimed antibodies, pharmaceutical compositions, and kits. Reconsideration and withdrawal of the rejection in

light of the following discussion is respectfully requested. Applicants submit that the Examiner has mischaracterized the disclosure of Combadiere et al (U.S. Patent Application Publication No. 2003/0195348) as outlined below.

For a prior art reference to anticipate a claimed invention, the prior art reference must teach each and every element of the claimed invention. *Lewmar Marine v. Barient* 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

The claimed invention is "[a]n isolated antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human chemokine receptor 5 (CCR5), wherein said antibody or antigen binding fragment inhibits binding of a chemokine to the receptor, wherein said chemokine is MIP-1α, MIP-1β, or RANTES, and wherein said antibody or antigen binding fragment thereof additionally inhibits HIV infection," or a pharmaceutical composition comprising such an antibody, or a test kit comprising such an antibody.

Applicants first point out that the only anti-CCR5 antibody actually made and used by Combadiere et al. is described in paragraph [0195] on page 20, namely "a rabbit polyclonal antiserum generated against a synthetic peptide representing the predicted extracellular amino terminal domain of CCR5 (amino acids 1-28)". In other words, the only antibody actually exemplified by Combadiere et al. was directed to the N-terminus of CCR5, and not the second extracellular loop. Furthermore, the Combadiere antibody was only used to monitor "cell surface expression" of CCR5 and a mutant CCR5 by flow cytometry. No determination was made as to whether the Combadiere antibody affected chemokine binding to CCR5 or HIV entry into cells through CCR5.

Thus, the Combadiere antibody, binding to the N-terminus of CCR5, does not include each and every element of the claimed invention, as (at the least) it does not bind to the second extracellular loop of CCR5.

Combadiere et al. generically mentions other antibodies or binding agents that bind CCR5, as the Examiner noted in the quoted section above. However, Applicants submit that the Examiner has mischaracterized the disclosure of Combadiere with respect to its teachings about CCR5 antibodies. Firstly, as described above, the only antibodies actually made and used by Combadiere were directed to the N-terminal 28 amino acids. In addition, Combadiere et al. does not teach "that their antibodies not only block HIV entry but also block binding of chemokines" as the Examiner purports, but *merely names or describes* a list of possible functions which hypothetical antibodies to CCR5 may or may not have, alone or in combination, in paragraph [0069]. In addition, the specification of Combadiere et al. does not specifically "teach raising antibodies against the second extracellular loop of CCR5", but rather suggests that a suitable antibody be directed against "at least one portion of an extracellular region of the CCR5 polypeptide, as shown in FIG.1", with such "extracellular regions" including the amino terminus of CCR5 as well as the first and third loops (please see Figure 1A and paragraph [0017], last sentence).

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Combadiere does not specifically point one of skill in the art to the second extracellular loop of CCR5, and in fact, as described above, the only antibody generated by Combadiere et al. was directed to amino acids 1-28 of CCR5 (the N-terminus).

Therefore, the antibody to CCR5 which was made and disclosed by Combadiere et al. does not include any or all of the limitations of the claimed invention, and so cannot anticipate the claimed invention. In addition, any other antibodies hypothetically described in Combadiere et al. were merely named or described, and do not form a teaching to one of skill in the art of an antibody that has all of the claimed characteristics of the antibodies now claimed (e.g., binds to the second extracellular loop of human CCR5, inhibits binding of MIP-1α, MIP-1β, or RANTES, and inhibits HIV infection), or pharmaceutical compositions or kits comprising them.

In view of all of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, Combadiere *et al.* (U.S. Patent Appln. Publication) fails to teach or suggest each and every element of the claimed invention expressly and/or inherently and, thus, Combadiere *et al.* fails to anticipate the claimed invention. For the foregoing reasons, this rejection of the claimed invention is believed to be improper and Applicants respectfully request that it be reconsidered and withdrawn.

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CONCLUSION

In view of the remarks made herein, Applicants respectfully submit that the rejections presented by the Examiner are now overcome and that this application is in condition for allowance. Applicants earnestly invite the Examiner to call the undersigned at (617) 679-7166, in order to discuss the rejections of record and this response.

This paper is being filed timely as a request for three month extension is filed concurrently herewith. Applicants believe no further extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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